

NOTICE OF ALLOWANCE

Claim Status

This action is in response to the papers filed on June 18, 2010. The claim amendments have been reviewed and entered. No new matter has been introduced. The Examiner contacted Applicant's representative Ms. Rebecca C. Riley Vargas on July 23, 2010 to discuss the amended claims filed on June 18, 2010 to place them in a better condition for allowance. The Examiner suggested amending claim 143 to incorporate the limitations of dependent claim 144 excluding an analyte and amending claim 155 to incorporate the limitations of dependent claim 156 excluding an analyte would place the remaining claims in condition for allowance. The Examiner further suggested cancelling withdrawn claims 112-115, 117, 128-129 and 130 because their scopes are different from claims 109, 127, 143 and 155. The examiner also suggested cancelling independent claim 131 and dependent claims 132-133 and 135-142 because the limitations of claim 131 are anticipated by Baez et al. Applicant's representative informed the Examiner that she would fax the proposed amendments to claims 143 and 155 directly to the Examiner.

The Examiner contacted the representative on August 23, 2010 to suggest amending claims 110, 122-123, 127, 143, 150-151, 155, 160, 162 and 163, changing the dependency of claim 160 from claim 155 to claim 159 to provide proper antecedent basis, and cancelling claim 158 because the scope of claim 154 would be identical to claim 146. The representative authorized changes on August 23, 2010 including cancellation of claims 112-115, 117, 128-133, 135-142, 144, 156 and 158. These

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amendments are included in the Examiner's amendments. Applicant's declaration and arguments filed on June 18, 2010 have been fully considered and are persuasive. The previous rejections in the office action dated December 18, 2009 are withdrawn. Claims 109-111, 119-127, 143, 145-155, 157, 159-165 and 166 are allowed subject to the Examiner's amendments listed below.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on January 28, 2010 and June 18, 2010 and were filed after the mailing date of the non-final action on December 18, 2009. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner.

Double Patenting Rejection - Withdrawn

The previous non-statutory obviousness type double patenting rejections of instant claims 109-111, 116, 119-127 and 131-142 over claims 1, 3-10 and 11 of copending application 11/836,339 in view of Egholm et al and Weston et al have been withdrawn because claims as amended are deemed non-obvious over the claims of '339 copending application.

The previous non-statutory obviousness type double patenting rejections of instant claims 109-111, 116, 119-127 and 131-142 over claims 1-7 and 9-18 of copending application 11/836,333 in view of Egholm et al and Weston et al have been

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withdrawn because claims as amended are deemed non-obvious over the claims of '333 copending application.

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Applicant's representative authorized the amendments on August 23, 2010. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it **MUST** be submitted no later than the payment of the issue fee.

Claims 109-111, 119-127, 143, 145-155, 157, 159-165 and 166 have been renumbered as Claims 1-33 according to 37 C.F.R. 1.126 (see MPEP 608.01 (j) and 608.01 (n) IV).

Claims 112-115, 117, 128-133, 135-142, 144, 156 and 158 are cancelled.

The claims are rewritten as follows.

Claim 110. The molecular biosensor of claim 109, wherein the target molecule is selected from the group consisting of a prion, a protein, a polypeptide, a nucleic acid, a lipid, a carbohydrate, a biomolecule, a macromolecular complex, a fungus, and a microbial organism.

Claim 122. The molecular biosensor of claim 109, wherein R2 and R6 are up to 500 angstroms in length.

Claim 123. The molecular biosensor of claim 109, wherein R2 and R6 are comprised of non-DNA polyethylene glycol and are up to 500 angstroms in length.

Claim 127. A molecular biosensor, the biosensor having two constructs, the constructs comprising:

R1-R2-R3-R4; and

R5-R6-R7-R8;

wherein:

R1 is an antibody epitope binding agent that binds to a first epitope on a target molecule;

R2 is a non-nucleic acid flexible linker attaching R1 to R3 by formation of a covalent bond with each of R1 and R3, wherein R2 comprises a bifunctional chemical crosslinker and is up to 500 angstroms in length;

R3 and R7 are a pair of complementary nucleotide sequences from about 4 to about 15 nucleotides in length and having a free energy for association over the entire length of the nucleotide sequence from about 5.5 kcal/mole to 8.0 kcal/mole at a temperature from about 21° C to about 40° C and at a salt concentration from about 1

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mM to about 100 mM, such that R3 and R7 only associate when R1 and R5 are bound to the target molecule;

R4 and R8 together comprise a detection means selected from the group consisting of FRET, fluorescence cross-correlation spectroscopy, fluorescence quenching, fluorescence polarization, flow cytometry, scintillation proximity, luminescence resonance energy transfer, direct quenching, ground-state complex formation, chemiluminescence energy transfer, bioluminescence resonance energy transfer, excimer formation, colorimetric substrates detection, phosphorescence, electro-chemical changes, and redox potential changes;

R5 is an antibody epitope binding agent that binds to a second epitope on the target molecule; and

R6 is a non-nucleic acid flexible linker attaching R5 to R7 by formation of a covalent bond with each of R5 and R7, wherein R6 comprises a bifunctional chemical crosslinker and is up to 500 angstroms in length.

Claim 143. A molecular biosensor, the biosensor having two constructs, the constructs comprising:

R1-R2-R3-R4; and

R5-R6-R7-R8;

wherein:

R1 is an epitope binding agent that binds to a first epitope on a target molecule selected from the group consisting of a prion, a protein, a polypeptide, a lipid, a

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carbohydrate, a biomolecule, a macromolecular complex, a fungus, and a microbial organism;

R2 is a non-nucleic acid flexible linker attaching R1 to R3;

R3 and R7 are a pair of complementary nucleotide sequences having a free energy for association, over the entire length of the nucleotide sequence, from about 5.5 kcal/mole to 8.0 kcal/mole at a temperature from about 21° C to about 40° C and at a salt concentration from about 1 mM to about 100 mM;

R4 and R8 together comprise a detection means such that when R3 and R7 associate a detectable signal is produced;

R5 is an epitope binding agent that binds to a second epitope on the target molecule; and

R6 is a non-nucleic acid flexible linker attaching R5 to R7.

Claim 150. The molecular biosensor of claim 143, wherein R2 and R6 are up to 500 angstroms in length.

Claim 151. The molecular biosensor of claim 143, wherein R2 and R6 are comprised of non-DNA polyethylene glycol and are up to 500 angstroms in length.

Claim 155. A molecular biosensor, the biosensor having two constructs, the constructs comprising:

R1-R2-R3-R4; and

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R5-R6-R7-R8;

wherein:

R1 is an antibody epitope binding agent that binds to a first epitope on a target molecule selected from the group consisting of a prion, a protein, a polypeptide, a lipid, a carbohydrate, a biomolecule, a macromolecular complex, a fungus, and a microbial organism;

R2 is a non-nucleic acid flexible linker attaching R1 to R3;

R3 and R7 are a pair of complementary nucleotide sequences having a free energy for association, over the entire length of the nucleotide sequence, from about 5.5 kcal/mole to 8.0 kcal/mole at a temperature from about 21° C to about 40° C and at a salt concentration from about 1 mM to about 100 mM;

R4 and R8 together comprise a detection means such that when R3 and R7 associate a detectable signal is produced;

R5 is an epitope binding agent that binds to a second epitope on the target molecule; and

R6 is a non-nucleic acid flexible linker attaching R5 to R7.

Claim 160. The molecular biosensor of claim 159, wherein the bonds are covalent bonds.

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Claim 162. The molecular biosensor of claim 155, wherein R2 and R6 are up to 500 angstroms in length.

Claim 163. The molecular biosensor of claim 155, wherein R2 and R6 are comprised of non-DNA polyethylene glycol and are up to 500 angstroms in length.

REASONS FOR ALLOWANCE

The following is an examiner's statement of reasons for allowance:

Applicant's declaration (pgs. 1-3), arguments (Remarks, pgs. 15-26) and supporting documents (pgs. 13-28) filed on June 18, 2010 are persuasive regarding the free energy calculation and claims as amended are not obvious over the cited prior art.

Instant claim 109 is drawn to a molecular biosensor having two constructs (R1-R2-R3-R4 and R5-R6-R7-R8), each having four different structural components, each construct having an epitope binding agent binding to different epitopes on the target molecule, each construct having complementary sequences over the entire length of the nucleotide sequence, bringing together said complementary nucleotide sequences associated with two constructs, wherein the free energy of association of the said nucleotide sequences is in the range of 5.5 Kcal/mole to 8.0 kcal/mole.

Instant claim 127 further defines the molecular biosensor of claim 109 requiring additional components, a bifunctional crosslinker up to 500 angstroms in length and a specific type of detection method as listed.

Instant claim 143 has the same structure of the molecular biosensor of claim 109 but requires R1 is an epitope binding agent that binds to a first epitope on a specific type of target molecules as listed and R5 is an epitope binding agent that binds to a second epitope on the specific type of target molecule as listed.

Instant claim 155 has the same structure of the molecular biosensor of claim 109 but requires R1 is an antibody epitope binding agent that binds to a first epitope on a specific type of target molecules as listed and R5 is an epitope binding agent that binds to a second epitope on the specific type of target molecule as listed.

Regarding instant claim 109, Egholm et al or Weston et al do not teach R1 and R5 are antibody epitope binding agents. Baez et al teaches antibody epitope binding agent but do not teach that the R3 and R7 are pair of complementary nucleotide sequence over the entire length of the nucleotide sequence. Applicant has also argued in the declaration that the free energy calculation based on the nearest neighbor analysis of Santa Lucia is not accurate (Declaration pg. 3). These arguments are persuasive.

Thus, the prior art of record taken alone or in combination does not suggest or obviate the molecular biosensor of claims 109, 127, 143 and 155, which requires two constructs each having four different structural components, each construct having an epitope binding agent binding to different epitopes on the target molecule, each construct having complementary sequences over the entire length of the nucleotide sequence, bringing together said complementary nucleotide sequences associated with two constructs, wherein the free energy of association of the said nucleotide sequences

is in the range of 5.5 Kcal/mole to 8.0 kcal/mole. Furthermore, none of the references of the record taken alone or in combination either teach or suggest the claimed molecular biosensor also in view of persuasive arguments made by the Applicant.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

Claims 109-111, 119-127, 143, 145-155, 157, 159-165 and 166 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Narayan K. Bhat whose telephone number is (571)-272-5540. The examiner can normally be reached on 8.30 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571)-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic

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Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Narayan K. Bhat/

Examiner, Art Unit 1634

/Robert T. Crow/

Primary Examiner, Art Unit 1634